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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,895	07/30/2003	John J. Rossi	1954-413	8585

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
08/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/629,895	ROSSI ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6 and 11-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/19/09 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, and 11-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agami et al. (US 7,241,618) taken with Doglio et al. (US 5,837,503) in further view of either Yu (AH) or Ambros (Cell, 2001, 107:823-6).

Agami et al. teach making and using an expression cassette comprising an adenoviral VA1 promoter operably linked to an siRNA molecule, wherein the siRNA molecule can be shRNA (columns 50-51 and Figures 8 and 10 and claim 3). Agami et al. teach that siRNA is a substrate for mammalian Dicer (columns 1-3). However, Agami does not specifically teach using RNAi in the vector, wherein the RNAi is precursor miRNA. In addition, Agami does not specifically teach the structural limitations of the claimed product set forth in claims 1 and 2.

However, at the time the invention was made, Doglio et al. teach an expression cassette comprising an oligonucleotide has been inserted between or outside the boxes A and B constituting the promoter of said VA gene or into VA1 gene (columns 8, 10-15, and 19-22).

Furthermore, at the time the invention was made, Yu teaches an RNA polymerase III vector comprising shRNA can inhibit expression in mammalian cells.

Also microRNA was well known to one of ordinary skill in the art as exemplified by Ambros (pages 823-826). Ambros teaches, "Animal genomes contain an abundance of small genes that produce regulatory RNAs of about 22 nucleotides in length (abstract)." "These microRNAs are diverse in sequence and expression patterns, and are evolutionary widespread, suggesting they may participate in a wide range of genetic regulatory pathways (abstract)."

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Agami taken with Doglio in further view of Yu and Ambros, namely to produce an expression cassette comprising an adenoviral VA1 promoter, wherein an RNAi molecule is contained within a non-essential stem region of the coding region of the VA1 gene. One of ordinary skill in the art would have been motivated to combine the teaching to avoid reducing the activity of the promoter or to determine if RNAi can reduce a target gene expressed in cells. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Agami taken with Doglio in further view of either Yu or Ambros, namely to produce a mammalian cell comprising the expression cassette comprising an adenoviral VA1 promoter, wherein an RNAi molecule is contained within a non-essential stem region of the coding region of the VA1 gene. One of ordinary skill in the art would have been motivated to combine

the teaching to avoid reducing the activity of the promoter or to determine if RNAi can reduce expression of a target gene in a cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/19/09 have been fully considered but they are not persuasive.

Applicant's arguments directed to that there is no motivation in the cited art to make such the claimed product because there is no reasonable expectation of success for the interfering RNA molecule that was inserted into the VA1 transcript would be cleaved out and become a substrate for Dicer, the argument is not found persuasive for the reasons set forth below and the arguments were previously addressed in the final rejection mailed on 1/5/09 (pages 5-6).

The Declaration under 37 CFR 1.132 filed 5/19/09 is insufficient to overcome the rejection of claims 1, 2, and 11-16 based upon 103(a) rejection as set forth in the last Office action because: the claimed invention is directed to a product that in view of the art of record teaching making the construct comprising a nucleic acid that inhibits gene expression would have been obvious to make the claimed product. The interfering RNAs taught in the art of record are efficient in RNAi response and target regions that are accessible to RISC. One of ordinary skill in the art would have been motivated to combine the teaching to avoid reducing the activity of the promoter or to determine if RNAi can reduce a target gene expressed in cells.

In response to applicant's argument that the examiner contends that it is not required that the RNAi molecule be cleaved out of the VA1 transcript because the transcript would be cleaved and become a substrate for Dicer as taught by Agami and Sharp, the applicant's interpretation of the examiner's statement is not correct and examiner apologizes for any confusion as the result of this statement because the examiner intended to indicate that the RNAi would be processed out of the VA1 transcript and become a substrate for Dicer, not the transcript including the RNAi molecule would become a substrate for Dicer . In view of the prior art of record (Sharp, Agami, and Brummelkamp, Science 296:550-553, 2002, of record, and Paddison et al. Genes Dev. 16:948-958, 2002) teaching how siRNA is processed from dsRNA (i.e., 70 nucleotides), one of ordinary skill in the art would reasonably expect the RNAi molecule would be cleaved out of the VA1 transcript and become a substrate for Dicer.

Claims 1, 2, and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami taken with Doglio in further view of either Yu or Ambros, as applied to claims 1, 2, and 11-16 above, and in further view of Cagnon et al. (AD).

Agami, Yu or Ambros taken with Doglio do not specifically teach the structural limitations of the VA1 promoter set forth in claim 3.

However, at the time the invention was made, Cagnon teaches inserting an RNAi molecule into a VA 1 expression cassette using a filled-in Not1 site that was ligated into the BstEII cleaved, filled in vector (page 252).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Agami taken with Yu, Ambros and Doglio in further view of Cagnon, namely to produce the expression cassette wherein the non-essential stem region contains a BstEII site. One of ordinary skill in the art would have been motivated to combine the teaching to clone the siRNA into the VA1 promoter of the expression cassette since the restriction site is found in an adenoviral VA1 promoter.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/19/09 have been fully considered but they are not persuasive.

Applicant's arguments directed to that there is no motivation in the cited art to make such the claimed product because there is no reasonable expectation of success for the interfering RNA molecule that was inserted into the VA1 transcript would be cleaved out and become a substrate for Dicer, the argument is not found persuasive for the reasons set forth below and the arguments were previously addressed in the final rejection mailed on 1/5/09 (pages 5-6).

The Declaration under 37 CFR 1.132 filed 5/19/09 is insufficient to overcome the rejection of claims 1, 2, and 11-16 based upon 103(a) rejection as set forth in the last Office action because: the claimed invention is directed to a product that in view of the art of record teaching making the construct comprising a nucleic acid that inhibits gene expression would have been obvious to make the claimed product. The interfering

RNAs taught in the art of record are efficient in RNAi response and target regions that are accessible to RISC. One of ordinary skill in the art would have been motivated to combine the teaching to avoid reducing the activity of the promoter or to determine if RNAi can reduce a target gene expressed in cells.

In response to applicant's argument that the examiner contends that it is not required that the RNAi molecule be cleaved out of the VA1 transcript because the transcript would be cleaved and become a substrate for Dicer as taught by Agami and Sharp, the applicant's interpretation of the examiner's statement is not correct and examiner apologizes for any confusion as the result of this statement because the examiner intended to indicate that the RNAi would be processed out of the VA1 transcript and become a substrate for Dicer, not the transcript including the RNAi molecule would become a substrate for Dicer . In view of the prior art of record (Sharp, Agami, and Brummelkamp, Science 296:550-553, 2002, of record, and Paddison et al. Genes Dev. 16:948-958, 2002) teaching how siRNA is processed from dsRNA (i.e., 70 nucleotides), one of ordinary skill in the art would reasonably expect the RNAi molecule would be cleaved out of the VA1 transcript and become a substrate for Dicer.

Claims 1, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Agami taken with Doglio in further view of either Yu or Ambros as applied to claims 1, 2, and 11-16 above, and further in view of Lorens (US 20040005593).

However, at the time the invention was made, Lorens teaches an RNAi molecule having a loop containing at least 6 nucleotide bases (page 7).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either Agami taken with either Yu or Ambros and Doglio in further view of Lorens, namely to produce an expression cassette comprising an adenoviral VA promoter, wherein an RNAi molecule comprises a loop containing about 8 nucleotide bases. One of ordinary skill in the art would have been motivated to combine the teaching to determine if there is an increase in the inhibition by using a common structure in a shRNA or precursor miRNA molecule to make the expression cassette.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 5/19/09 have been fully considered but they are not persuasive.

Applicant's arguments directed to that there is no motivation in the cited art to make such the claimed product because there is no reasonable expectation of success for the interfering RNA molecule that was inserted into the VA1 transcript would be cleaved out and become a substrate for Dicer, the argument is not found persuasive for the reasons set forth below and the arguments were previously addressed in the final rejection mailed on 1/5/09 (pages 5-6).

The Declaration under 37 CFR 1.132 filed 5/19/09 is insufficient to overcome the rejection of claims 1, 2, and 11-16 based upon 103(a) rejection as set forth in the last Office action because: the claimed invention is directed to a product that in view of the art of record teaching making the construct comprising a nucleic acid that inhibits gene

expression would have been obvious to make the claimed product. The interfering RNAs taught in the art of record are efficient in RNAi response and target regions that are accessible to RISC. One of ordinary skill in the art would have been motivated to combine the teaching to avoid reducing the activity of the promoter or to determine if RNAi can reduce a target gene expressed in cells.

In response to applicant's argument that the examiner contends that it is not required that the RNAi molecule be cleaved out of the VA1 transcript because the transcript would be cleaved and become a substrate for Dicer as taught by Agami and Sharp, the applicant's interpretation of the examiner's statement is not correct and examiner apologizes for any confusion as the result of this statement because the examiner intended to indicate that the RNAi would be processed out of the VA1 transcript and become a substrate for Dicer, not the transcript including the RNAi molecule would become a substrate for Dicer . In view of the prior art of record (Sharp, Agami, and Brummelkamp, Science 296:550-553, 2002, of record, and Paddison et al. Genes Dev. 16:948-958, 2002) teaching how siRNA is processed from dsRNA (i.e., 70 nucleotides), one of ordinary skill in the art would reasonably expect the RNAi molecule would be cleaved out of the VA1 transcript and become a substrate for Dicer.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635